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57. A method for treating an apoptosis related condition in a mammal, comprising administering a recombinant nucleic acid according to any one of Claims 35-37.--

REMARKS

Claims 1-34 have been cancelled, without prejudice, disclaimer, or admission. Claims 35-57, drawn to the subject matter of elected Group I (Claims 1-17, 30 and 32) have been added, and consideration of these new claims is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current Amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Rejections under 35 U.S.C. §112, first paragraph (written description)

Claims 1-17, 30 and 32 stand rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the written description requirement. Applicants respectfully traverse.

Preliminarily, Applicants point out that the new claims drawn to nucleic acid sequences include claims directed to nucleic acid sequences having at least 90% identity to SEQ ID NO:1, rather than 70% identity as previously claimed.

Similarly, new claims drawn to amino acid sequences include claims directed to amino acid sequences having at least 90% identity to SEQ ID NO:2, rather than 70% identity as previously claimed.

Regarding SEQ ID NOs: 3-21, the Office Action states that the relationship of these sequences to TOSO sequence (SEQ ID NO:1) is unclear. Applicants respectfully

point out that SEQ ID NOs: 3-21 occur in Figure 3, which depicts a sequence alignment of fragments of TOSO nucleic acid sequence (i.e. segments of SEQ ID NO:1) and other nucleic acid sequences identified in a BLAST search for identity to TOSO nucleic acid sequence. The correspondence of TOSO fragments to SEQ ID NO:1 is clearly depicted, and the correspondence of other nucleic acid sequences set forth in Figure 3 to SEQ ID NO:1 is clearly depicted. Thus, the relationship of SEQ ID NOs: 3-21 to SEQ ID NO:1 is clearly described in the instant specification.

Further, Applicants respectfully point out that the present claims are not directed to SEQ ID NOs: 3-21, rather they are directed in part to sequences having at least 90% sequence identity to SEQ ID NO:1 and SEQ ID NO:2, or defined portions thereof as described below. The meaning of "sequence identity" is generally described at page 10, line 10 of the specification. Additionally, new claims are directed in part to nucleic acids capable of hybridizing to SEQ ID NO:1. The meaning of "hybridization" is generally described in the specification at page 13, beginning at line 22.

With regard to the fragments of SEQ ID NO:2 to which the present claims are directed, Applicants point out that the specification clearly describes the following segments of SEQ ID NO:2:

(i) amino acids 18-253, comprising the extracellular domain of TOSO protein, page 10, line 23; and

(ii) amino acids 273-390, comprising the cytoplasmic domain of TOSO protein, page 11, line 6, and page 10, line 22.

In addition, at page 16, line 18, the specification sets forth an amino acid sequence variant comprising the extracellular domain in a preferred embodiment.

The Office Action refers to the interim guidelines for determining satisfaction of the written description requirement (Federal Register, Volume 64, Number 244, page 71427-71440). Applicants respectfully direct the Examiner to the following passages of these guidelines.

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Section II. A.

> There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. ... Consequently, rejection of an original claim for lack of written description should be rare.

Further, at II. A. 1, the guidelines state:

> The examiner should evaluate each claim to determine if sufficient structures, acts, or functions are recited to make clear the scope of and meaning of the claim ...

Regarding the demonstration of possession of the invention, the guidelines further state at Section II. A. 3a:

> Possession may be shown in any number of ways. ... or by a written description of the invention describing sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention.

In connection with the rejection, the Office Action expresses that the written description is satisfied only for nucleic acids comprising the sequence set forth by SEQ ID NO:1, and for polypeptides comprising the amino acid sequence set forth by SEQ ID NO:2. Applicants respectfully disagree.

Regarding genus claims, the interim guidelines state the following:

> The written description may requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by ... disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties...sufficient to show the applicant was in possession of the claimed genus.

Further, the guidelines state:

> Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

The essential purpose of the written description requirement is to show the possession of the invention as of the filing date as a *prima facie* date of invention. In re Smith, 481 F.2d 910, 178 U.S.P.Q. 620,623 (CCPA 1973). Accordingly, the specification is required to contain a statement that adequately describes the invention as claimed. However, the invention need not be described in *ipsis verbis* in order to satisfy the description requirement. See In re Lukach, Olson, and Spurlin, 169 U.S.P.Q. 795, 796 (CCPA 1971).

Accordingly, the written description requirement does not require that the actual sequence of all nucleic acids of the instant invention be recited. Use of the terms "hybridizing to" and "90% identity to" are sufficient to convey to the reasonably skilled artisan a clear conception of the invention.

Applicants submit that the invention is described by the specification in such a manner as to convey to the reasonably skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed. Applicants further submit that a prima facie case of lack of written description has not been established. As such, Applicants respectfully request withdrawal of the rejection as it pertains to the new claims, and request allowance of the new claims.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 1-17, 30 and 32 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. Applicants respectfully traverse.

Preliminarily, Applicants point out that the new claims drawn to nucleic acid sequences include claims directed to nucleic acid sequences having at least 90% identity to SEQ ID NO:1, rather than 70% identity as previously claimed.

Similarly, new claims drawn to amino acid sequences include claims directed to amino acid sequences having at least 90% identity to SEQ ID NO:2, rather than 70% identity as previously claimed.

Further, in the interest of advancing prosecution, Applicants have addressed the concern expressed in the Office Action regarding use of the term "TOSO protein" and have not used the term in the new claims.

The Office Action expresses that enablement is lacking for amino acid sequences differing from SEQ ID NO:2, for instance by a single residue, because polypeptides so encoded may have activities different from that of a protein corresponding to SEQ ID NO:2. Applicants respectfully disagree.

Applicants point out that to satisfy the enablement requirement of 35 U.S.C. §112, the specification must enable the reasonably skilled artisan to make and use the invention commensurate in scope with the claims without undue experimentation.

Applicants submit that disclosure of methods for determining hybridization (page 13, line 22), as well as methods for determining sequence identity (page 10, line 11), in conjunction with the sequences provided (SEQ ID NO:1 and SEQ ID NO:2) enable the reasonably skilled artisan to make and use the invention in full scope of the claims. As such, Applicants submit that the specification satisfies the enablement requirement of §112.

Moreover, Applicants point out that amino acid sequence variants of SEQ ID NO:2 are considered in the present application. At page 15, beginning at line 21, the specification describes amino acid sequence variants falling within the scope of the invention. The specification describes the types of amino acid substitutions occurring (conservative and non-conservative) and the effects that such substitutions have on the activity of variants. Further, at page 16, line 4, the specification sets forth amino acid sequence variants having modified characteristics in a preferred embodiment.

As established in *In re: Wands*, the amount of guidance given in a specification, and the inclusion of working examples, are both factors that may be considered in determining enablement.

Applicants submit that the guidance given in the specification regarding methods for determining sequence identity and nucleic acid hybridization, in conjunction with TOSO nucleic acid and amino acid sequences (SEQ ID NOs:1 and 2 respectively) disclosed, enables the reasonably skilled artisan to make and use the invention in full scope of the new claims. Further, the Examples given concerning methods for determining the activity of amino acid variants support a finding of enablement for the new claims. Applicants respectfully request withdrawal of the rejection as it pertains to the new claims, and request allowance of the new claims directed to the subject matter of old Claims 1-17.

Regarding Claim 30, the Office Action expresses that a method for modulating apoptosis in a cell other than a T cell is not enabled. In addition, regarding Claim 32, the Office Action expresses that a method for treating an apoptosis related condition in a mammal using a TOSO protein is not enabled.

The Office Action recites excerpts from several review articles concerning gene therapy to support the position that the art of gene therapy is highly unpredictable. The Office Action further expresses that enablement requires that the specification provide suitable guidance or examples to help the artisan deal with the hurdles recognized to exist in the practice of gene therapy. Applicants respectfully disagree.

While the exploitation of gene therapy generally may require more developmental work, this is not the standard for patentability. Applicants point out that the standard for enablement under 35 U.S.C. §112 is that the specification fully enables one skilled in the art to make and use the invention without undue experimentation. Applicants further submit that the specification, considered in conjunction with the state of the art at the time the present application was filed, supports enablement of Claims 30 and 32.

First, as discussed above, the specification sets forth the sequences to be used to modulate apoptosis or treat an apoptosis related disorder. Second, a therapeutically effective dose of TOSO nucleic acid is considered at page 29, line 16. Third, the

recipients of TOSO nucleic acids, i.e. patients, are considered at page 29, line 26. Fourth, methods of introducing TOSO nucleic acids into mammalian cells are disclosed at page 24, line 23.

In addition, reports of the successful practice of gene therapy exist. For example, Roth et al, Nature Medicine 2(9):985-991, 1996 (enclosed as Exhibit A), disclose the successful use of p53 gene transfer to cancer patients, with tumor regression and tumor stabilization reported.

The Office Action expresses further concern that the activity of TOSO protein may be restricted to T cells based on expression analysis and dependence of TOSO activity on the T cell receptor signal transduction pathway.

In response, Applicants point out that TOSO mRNA was detected in hematopoietic cells other than T cells (page 45, line 13; page 44, line 18). Further, Example 2 discloses that forced expression of TOSO mRNA is sufficient to inhibit apoptosis induced by FAS stimulation, FADD expression, exposure to TNF-α, and ionomycin/PMA. This suggests that TOSO activity does not depend on T cell receptor signaling. Moreover, this apoptosis-inhibiting activity was observed in B cells as well as T cells (page 45, lines 19-21).

The Examiner's attention is respectfully directed to M.P.E.P. §2164.04:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . A specification disclosure which contains a teaching of the manner and process of making an using an invention which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

As stated by the court in In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a

supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (Emphasis added).

Applicants respectfully submit that a *prima facie* case of lack of enablement has not been demonstrated. Accordingly, Applicants respectfully request withdrawal of the rejections as they pertain to the new claims, and request allowance of the new claims.

If, upon review, the Examiner feels that there are any additional outstanding issues, the applicants respectfully request that the Examiner call the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON HERBERT LLP

Dated: 19 April 2001

By _____
David J. Brezner
Reg. No. 24,774

Four Embarcadero Center - Suite 3400
San Francisco, California 94111-4187
Tel.: (415) 781-1989
Fax: (415) 398-3249

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

~~1. A recombinant nucleic acid encoding a Toso protein that will hybridize under high stringency conditions to the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1) or its complement.~~

~~2. A recombinant nucleic acid encoding a Toso protein that is at least about 70% identical to the amino acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~3. A recombinant nucleic acid according to claim 2 that is at least about 70% identical to the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1) or its complement.~~

~~4. A recombinant nucleic acid according to claim 1 wherein said Toso protein is a human Toso protein.~~

~~5. A recombinant nucleic acid according to claim 1 encoding the amino acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~6. A recombinant nucleic acid according to claim 1 encoding a Toso polypeptide that is at least about 70% identical to the sequence of amino acid residues 18 to 253 of Figure 2a (SEQ ID NO:2).~~

~~7. A recombinant nucleic acid according to claim 1 having at least 70% sequence identity to (a) a DNA molecule encoding a Toso polypeptide comprising the sequence of amino acid residues 18 to 253 of Figure 2a (SEQ ID NO:2), or (b) the complement of the DNA molecule of (a).~~

~~8. A recombinant nucleic acid according to claim 1 encoding a Toso polypeptide that is at least about 70% identical to the sequence of amino acid residues 18 to 272 of Figure 2a (SEQ ID NO:2)~~

~~9. A recombinant nucleic acid according to claim 1 having at least 70% sequence identity to (a) a nucleic acid molecule encoding a Toso polypeptide comprising the sequence of amino acid residues 18 to 272 of Figure 2a (SEQ ID NO:2), or (b) the complement of the nucleic acid molecule of (a).~~

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

~~1. A recombinant nucleic acid encoding a Toso protein that will hybridize under high stringency conditions to the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1) or its complement.~~

~~2. A recombinant nucleic acid encoding a Toso protein that is at least about 70% identical to the amino acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~3. A recombinant nucleic acid according to claim 2 that is at least about 70% identical to the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1) or its complement.~~

~~4. A recombinant nucleic acid according to claim 1 wherein said Toso protein is a human Toso protein.~~

~~5. A recombinant nucleic acid according to claim 1 encoding the amino acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~6. A recombinant nucleic acid according to claim 1 encoding a Toso polypeptide that is at least about 70% identical to the sequence of amino acid residues 18 to 253 of Figure 2a (SEQ ID NO:2).~~

~~7. A recombinant nucleic acid according to claim 1 having at least 70% sequence identity to (a) a DNA molecule encoding a Toso polypeptide comprising the sequence of amino acid residues 18 to 253 of Figure 2a (SEQ ID NO:2), or (b) the complement of the DNA molecule of (a).~~

~~8. A recombinant nucleic acid according to claim 1 encoding a Toso polypeptide that is at least about 70% identical to the sequence of amino acid residues 18 to 272 of Figure 2a (SEQ ID NO:2)~~

~~9. A recombinant nucleic acid according to claim 1 having at least 70% sequence identity to (a) a nucleic acid molecule encoding a Toso polypeptide comprising the sequence of amino acid residues 18 to 272 of Figure 2a (SEQ ID NO:2), or (b) the complement of the nucleic acid molecule of (a).~~

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~~10. A recombinant nucleic acid according to claim 1 encoding a Toso polypeptide that is at least about 70% identical to the sequence of amino acid residues 273 to 390 of Figure 2a (SEQ ID NO:2).~~

~~11. A recombinant nucleic acid according to claim 1 comprising DNA having at least 70% sequence identity to (a) a nucleic acid molecule encoding a Toso polypeptide comprising the sequence of amino acid residues 273 to 390 of Figure 2a (SEQ ID NO:2), or (b) the complement of the nucleic acid molecule of (a).~~

~~12. A recombinant nucleic acid according to claim 1 operably linked to control sequences recognized by a host cell transformed with the nucleic acid.~~

~~13. An expression vector comprising the nucleic acid of claim 12.~~

~~14. A host cell comprising the recombinant nucleic acid of claim 1.~~

~~15. A host cell comprising the vector of claim 13.~~

~~16. A process for producing a Toso protein comprising culturing the host cell of claim 14 under conditions suitable for expression of a Toso protein.~~

~~17. A process according to claim 16 further comprising recovering said Toso protein.~~

~~18. A Toso protein encoded by a nucleic acid that will hybridize under high stringency conditions to the complement of the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~19. A recombinant Toso protein that is at least about 70% identical to the amino acid sequence depicted in Figure 2a (SEQ ID NO:2).~~

~~20. A Toso protein according to claim 18 comprising the sequence depicted in Figure 2a (SEQ ID NO:2).~~

~~21. A Toso protein according to claim 18 encoded by a nucleic acid at least about 70% identical to the nucleic acid sequence depicted in Figure 1 (SEQ ID NO:1).~~

~~22. An isolated polypeptide which specifically binds to a Toso protein according to claim 18.~~

~~23. A polypeptide according to claim 22 that is an antibody.~~

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~~24. A polypeptide according to claim 23 wherein said antibody is a monoclonal antibody.~~

~~25. A monoclonal antibody according to claim 24 that modulates the biological function of a Toso protein.~~

~~26. A monoclonal antibody according to claim 25 that reduces or eliminates the biological function of a Toso protein.~~

~~27. A monoclonal antibody according to claim 24 that increases the biological function of a Toso protein.~~

~~28. An antibody according to claim 23 directed against the extracellular domain of the Toso protein comprising the sequence of amino acid residues 18 to 253 of Figure 2a (SEQ ID NO:2).~~

~~29. An antibody according to claim 23 directed against the cytoplasmic domain of the Toso protein comprising the sequence of amino acid residues 273 to 390 of Figure 2a (SEQ ID NO:2).~~

~~30. A method of modulating apoptosis in a cell comprising administering to said cell a recombinant nucleic acid encoding a Toso protein.~~

~~31. A mammalian cell comprising a modified Toso cell surface receptor.~~

~~32. A method for treating an apoptosis related condition in a mammal comprising administering a recombinant nucleic acid encoding a Toso protein.~~

~~33. A method for treating an apoptosis related condition in a mammal comprising administering a Toso protein.~~

~~34. A method for treating an apoptosis related condition in a mammal comprising administering an anti-Toso antibody.~~

35. A recombinant nucleic acid, that will hybridize under high stringency conditions to a nucleic acid comprising the nucleic acid sequence set forth in SEQ ID NO:1 or its complement.

36. A recombinant nucleic acid, comprising a nucleic acid sequence having at least about 90% identity to the nucleic acid sequence set forth in SEQ ID NO:1.

37. A recombinant nucleic acid, comprising a nucleic acid sequence encoding an amino acid sequence having at least about 90% identity to the amino acid sequence set forth in SEQ ID NO:2.

38. A recombinant nucleic acid according to Claim 35, wherein said recombinant nucleic acid further comprises the nucleic acid sequence set forth in SEQ ID NO:1.

39. A recombinant nucleic acid according to Claim 37, wherein said nucleic acid sequence encodes the amino acid sequence set forth in SEQ ID NO:2.

40. A recombinant nucleic acid according to Claim 35, wherein said recombinant nucleic acid encodes a human protein.

41. A recombinant polypeptide, comprising an amino acid sequence having at least about 90% identity to the amino acid sequence set forth in SEQ ID NO:2.

42. A recombinant polypeptide, comprising an amino acid sequence encoded by a recombinant nucleic acid according to Claim 35.

43. A recombinant polypeptide according to Claim 41, further comprising the amino acid sequence set forth by SEQ ID NO:2.

44. A recombinant polypeptide according to Claim 41, wherein said amino acid sequence corresponds to the amino acid sequence of a human protein.

45. A recombinant nucleic acid according to Claim 35, further comprising a nucleic acid sequence encoding an amino acid sequence having at least 90% identity to the amino acid sequence set forth by amino acids 18-253 of SEQ ID NO:2, or the complement of said nucleic acid sequence.

46. A recombinant nucleic acid according to Claim 45, wherein said nucleic acid sequence encodes the amino acid sequence set forth by amino acids 18-253 of SEQ ID NO:2.

47. A recombinant nucleic acid according to Claim 35, further comprising a nucleic acid sequence encoding an amino acid sequence having at least 90% identity to the amino acid sequence set forth by amino acids 273-390 of SEQ ID NO:2, or the complement of said nucleic acid sequence.

48. A recombinant nucleic acid according to Claim 47, wherein said nucleic acid sequence encodes the amino acid sequence set forth by amino acids 273-390 of SEQ ID NO:2.

49. A recombinant nucleic acid according to any one of Claims 35-37, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the nucleic acid.

50. An expression vector, comprising the nucleic acid of Claim 49.

51. A host cell, comprising the recombinant nucleic acid of any one of Claims 35-37.

52. A host cell, comprising the expression vector of Claim 50.

53. A method for producing a protein, comprising culturing the host cell of Claim 51 under conditions suitable for expression of a protein.

54. A method for producing a protein, comprising culturing the host cell of Claim 52 under conditions suitable for expression of a protein.

55. A method according to either Claim 53 or Claim54, further comprising recovering said protein.

56. A method for modulating apoptosis in a cell, comprising administering to said cell a recombinant nucleic acid according to any one of Claims 35-37.

57. A method for treating an apoptosis related condition in a mammal, comprising administering a recombinant nucleic acid according to any one of Claims 35-37.